Visual evoked potentials

Latency of the mfVEP to diagnose glaucoma?

M Bach

The multifocal approach is a truly innovative technique

Correct identification of early dysfunction, before the onset of irreversible glaucomatous damage, is a holy grail in glaucoma research. Rodarte *et al*, in this issue of *BJO* (p 1132), present a predominantly negative report in that respect.[1] While disappointing, negative results are vitally important and often fall prey to publication bias.[2 3] Of the many approaches including morphological imaging and functional testing, these authors used an advanced electrophysiological technique, specifically the multifocal visual evoked potential (mfVEP).[4] Visual electrophysiology assesses, step by step, the function of the visual processing chain. It has progressed from its classic arsenal of ''three letter examinations'' (ERG, electroretinogram[5]; EOG, electro-oculogram[6]; VEP, visual evoked potential[7]) to four (PERG, pattern ERG[8]) and five letter methods (mfERG[9]/mfVEP, mf representing ''multifocal'').

Although each of these techniques test a different and specific stage of the visual processing chain (the EOG—for example, the function of the retinal pigment epithelium), all of them have been applied in glaucoma, reportedly successful at that, even the EOG (seen on an ARVO poster, but a Diamox response has been demonstrated[10]). Significant findings may, of course, represent spurious chance or tiny effects, raised to arbitrary significance values either by choosing advanced disease stages or by including a very high number of participants in group comparisons.

The multifocal approach, mostly applied to the ERG,[11] but also to pupillary responses,[12] is a truly innovative technique[13 14] to probe the central plus or minus 30° of the visual field quasi-simultaneously, resulting in a functional map of responses either locally on the retina (mfERG) or of the entire visual pathway (mfVEP). To aid the non-specialist readers, who by now will have had their measure of acronyms: when summing over all local responses, the mfVEP becomes rather similar to the normal, or ''classic'' VEP.

The multifocal VEP has been repeatedly demonstrated to be of some use in glaucoma as an objective form of perimetry.[15] Given that the amplitudes or an appropriate signal to noise measure is the main variable, what motivated Hood's group[1] to look at latencies of the mfVEP responses in glaucoma patients? Parisi *et al*[16] recently reported 100% sensitivity and 100% specificity in diagnosing glaucoma patients based on (classic) VEPs. Strong stuff. Early local damage might even be more apparent at appropriate locations in the mfVEP, so Rodarte and colleagues evaluated the mfVEP in 47 normal controls, 25 high tension glaucoma, and 25 normotensive glaucoma patients. Their main outcome variable was latency, looking at differences between groups and interocular differences.

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The results show rather little increase of latency in glaucoma, certainly not in the range that would markedly benefit in individual assessment. Of the receiver operating space they report a point with 30% sensitivity and 87% specificity. (I will not discuss the interocular comparison, which performs slightly better, but depends on chance differences between the eyes.)

What an exciting situation: a major discrepancy in the reports from two well known groups! Glaucoma stage does not seem to have differed too much between these two studies. Of course, there are major methodological differences: in visual field extent of the stimuli, in their spatial frequency content in the temporal parameters, etc. None of these can consistently explain the differing results to me: the higher temporal frequency used in the multifocal approach should make the method more sensitive to glaucomatous changes.[17 18] In addition to the VEP, Parisi *et al*[16] also recorded the PERG in their patients. The PERG, as a direct correlate of ganglion cell function, would be expected to be a good surrogate marker for glaucoma. Indeed, they also report 100% sensitivity and 100% specificity for the P50-N95 amplitude of the PERG. In my laboratory, the PERG indeed is a strong predictor of progression in glaucoma but never with perfect accuracy.[18–20] While there may be shortcomings in our methods, this suggests to me that Parisi *et al* had an auspicious patient group. We eagerly await further developments in this field, especially to discover whether studies combining PERG, VEP, and mfVEP, in well defined patient groups, may bring us nearer to said holy grail.

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Visual evoked potentials

The effects of glaucoma on the latency of the multifocal visual evoked potential

S L Graham

Delays in signal conduction are not great enough to be useful clinically

In this issue of the *BJO* (p 1132) the paper by Rodarte *et al* reports on the effect of glaucoma on the multifocal multichannel visual evoked potential (mfVEP), specifically its effect on signal latency.[1] Many previous publications have established that there is a loss of mfVEP amplitude in glaucoma.[2–5] This paper confirms that there are also some measurable effects on latency, but the delays in signal conduction are not great enough to be useful clinically with only 40% showing significant change. As a relative negative finding this is important if the mfVEP is to be used in the diagnostic setting.

It is consistent with our understanding of the mechanisms of cell death in glaucoma, where demyelination is not a feature, in contrast to optic neuritis where marked latency delays are the hallmark. In fact in our recent study,[6] large mfVEP latency delays in the recovery phase of a first episode of optic neuritis may even be predictive of the later onset of multiple sclerosis. A recent paper by Danesh-Meyer *et al* has also reported mfVEP amplitude reductions in compressive optic neuropathy,[7] with some latency delays but not as marked as in optic neuritis (personal communication). The relative losses of amplitude versus delay may help separate not only disease types, but possibly prognosis in these conditions. It had been hoped that latency delays in glaucoma may be useful as an early marker in glaucoma, since there are many previous studies on the conventional VEP (cVEP) where some delays were identified. Also, latency has greater reproducibility and less inter-subject variability so would therefore be a useful parameter to measure. Unfortunately, this study confirms that the delays are not substantial enough to use in diagnosis. We had previously found similar results with the Veris (Electro-Diagnostic Imaging, San Mateo, CA, USA) multifocal system using quadrantic latency averages,[8] and also with the AccuMap system (ObjectiVision, Sydney, Australia) with individual latencies.[9]

Many papers have examined the cVEP in glaucoma and identified latency changes.[10 11] In an early study with an age corrected cohort of patients with open angle glaucoma (OAG) and ocular hypertension (OHT), the full field pattern VEP showed about 50% and 25% of patients, respectively, to have a delay in latency compared to normals.[12] The predominant effect in other studies was a delay in p100 latency of around 20 ms[12 13] and a phase shift in the steady state pattern visually evoked potential (PVEP).[14 15] Horn *et al* reported that the peak time of a blue-yellow VEP had high sensitivity, and could be used to monitor progression.[16] The consensus appears to be that for the cVEP there is definitely some delay detected, but the ability of the tests to reliably separate glaucoma from normals varies greatly between studies.

> The amplitude of the mfVEP shows substantial reductions in glaucoma but latency delays are only mild

Rodarte *et al* in the current study raise the point that their results seem to be in contrast to a recent paper on cVEPs[17] where extremely high sensitivity and specificity (100%) for the latency of the VEP in glaucoma was reported. It is interesting to note in that paper that even the OHT subjects (IOP >21 mm Hg but normal discs) were also all delayed and clearly demarcated from the controls. This implies very early pressure related dysfunction in a group that may not all be destined for clinical glaucoma, yet the mfVEP only identified minor delays in established glaucoma.

There is no clear explanation for the difference in the findings of these two reports, but clearly it is important to conduct a study to compare the two types of VEP (conventional and multifocal) in the same individuals with early glaucoma. This should help confirm known differences between the two tests and establish if there is a difference in the effects of glaucoma on latency.

Fortune and Hood[18] have already done a comparative study in normals and shown that transient pattern reversal cVEP responses to relatively large field stimuli cannot be related simply to the sum of local mfVEP responses recorded with fast m-sequence stimulation. The amplitude of the full field response grew dramatically as the sequence was slowed, which was the result of several factors, including loss of hemifield polarity inversion, increased dominance of the lower hemifield, and overall growth in amplitude with slower reversal rates.

The cVEP is dominated by the central macular responses, and the lower central field more than upper, depending on electrode position. It is recorded with a uniform stimulus check size and a slow reversal rate throughout the field. It is a summed response from multiple striate cells of different orientation, and there can be different cancellation effects depending on the individual's underlying cortical convolutions. This may be why many previous full field studies have failed to show consistent amplitude loss in glaucoma, as location of the field loss (peripheral versus central, or superior versus inferior) may produce different effects on the net recorded response.[2] It could also theoretically change the latency, as the shape and timing of the waveforms differ in different parts of the field, unlike the electroretinogram (ERG) which has the same shaped waveform throughout.

There are several differences between the two test techniques, which could contribute to differing results. The mfVEP dartboard stimulus is cortically scaled, with larger checks in the periphery and smaller checks in the centre, to